REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 30-47 and 50 will be pending in the application. Claims 1-29, 48-49 and 51 are cancelled with the present amendment as drawn to non-elected inventions. Claims 32, 24-27, 39-40, 42-47 and 50 are amended herein to correct antecedent basis and insert the appropriate SEQ ID NOs as requested by the Examiner. The specification has also been amended to insert the appropriate SEQ ID NOs and correct typographical and clerical errors as requested by the Examiner.

No new matter is added by these amendments. The cancellation of claimed subject matter of does not constitute an admission by Applicants that the subject matter no longer claimed is not patentable. Applicants reserve the right to pursue all cancelled subject matter in a continuing application or applications.

Applicants acknowledge with appreciation that the Examiner has indicated that claims 44-46 are free of the prior art.

OBJECTIONS

Specification:

The Examiner has requested that Applicants insert SEQ ID NOs in the specification and claims in compliance with the sequence listing rules. Applicants have herein amended the specification and pending claims to insert the appropriate SEQ ID NOs.

REJECTIONS

Rejections under 35 U.S.C. 112, Second Paragraph

Claim 50 has been rejected as being indefinite. The Examiner states that claim 50 lacks antecedent basis in base claim 31. Applicants have amended claim 50 to properly depend from claim 43 and as such this rejection is now moot and should be withdrawn.

Rejections under 35 U.S.C. 103

A. Claims 30-43 stand rejected under 35 U.S.C §103 as being unpatentable over Kuby et al. (herein referred to as "Kuby") in view of Aridor et al. (herein referred to as "Aridor") and U.S. Pat. No. 5,807,746 to Lin (hereafter referred to as "Lin").

Motivation to Combine:

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; and (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention.[1] The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention.[2] The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification.[3]

The Examiner states that while Kuby does not teach a cell importation peptide linked to a mast cell degranulation inhibitor peptide to treat allergies, Kuby does disclose that the inhibition of mast cell degranulation is a known mechanism to treat allergies (*See*, Office Action at page 3). The Examiner also states that although Aridor teaches the peptide KNNLKECGLY and its use in inhibiting mast cell degranulation when given to permeabilized cells, Aridor also teaches that the peptide was ineffective in inhibiting mast cell degranulation in intact cells (*See*, Office Action at page 3). The Examiner completes the rejection by stating that Lin teaches adding the sequence AAVALLPAVLLALLAP to any biologically active peptide to the allow transportation of the active peptide to the inside of the cell in vivo by teaching administering the peptides orally (*See*, Office Action at page 3). Since treating allergies with mast cell degranultor inhibitors was well known in the art as taught by Kuby, and the use of the Aridor peptide suffered from its inability to be transported across he cell membrane, a deficiency which was cured by Lin, the Examiner asserts that one of skill in the art would have been motivated to add the importation peptide of Lin to the mast cell degranulation inhibitor of Aridor based on the teachings of Kuby (*See*, Office Action at page 3). Applicants traverse.

Claim 30, from which claims 31-47 and 50 properly depend, is drawn to a method of **treating an allergic condition in a subject** by administering a therapeutic agent, where the agent comprises a molecule having a first segment competent for importation of the molecule **into mast cells *in vivo*** and a second segment for having **an anti-allergic effect within mast cells**, where the first segment and second segment are joined through a linker, and the molecule is capable of **exerting its anti-allergic effect *in vivo*** (Emphasis added). For the reasons discussed *infra*, Applicants submit that it would not have been obvious to one of ordinary skill

[1] *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).
[2] *In re Napier*, 55 F.3d 610 (Fed. Cir. 1995).

in the art to administer the therapeutic molecule of the instant invention into mast cells *in vivo* to treat an allergic condition in a subject, as the claimed invention is directed to a) *in vivo* administration, b) administration into mast cells and c) methods of treating an allergic condition in a subject *in vivo*. The combination of Kuby, Aridor and Lin does not produce the claimed invention nor does it contain a suggestion or motivation to combine the references in such a way to achieve the claimed invention.

Kuby generally discloses drug therapies which have been shown to block mast cell degranulation by interfering with various biochemical steps in mast cell activation by interacting with receptors and electrolyte influx at the mast cell plasma membrane (*See*, Kuby column 2; Table 16-7). While Kuby discloses mast cells and various drug therapies, Kuby does not teach or suggest a therapeutic agent comprising a molecule having at least a first segment competent for importation of the molecule *in vivo* or methods of treating an allergic condition in a subject *in vivo* using the therapeutic agent. Moreover, since Kuby discloses numerous drug therapies which are successful in inhibiting mast cell degranulation, the skilled artisan reading Kuby would not be motivated to improve the current therapies for mast cell degranulation and certainly would not be motivated to use the reference to achieve the claimed invention.

Similar to Kuby, Aridor does not teach or suggest therapeutic agent comprising a molecule having at least a first segment competent for importation of the molecule *in vivo* or methods of treating an allergic condition in a subject *in vivo* using the therapeutic agent. Aridor only discloses inhibition of exocytosis by the introduction of a Gai_3 peptide to permeabilized mast cells *in vitro*. As indicated by the Examiner, Aridor teaches that the Gai_3 peptide was ineffective when added to intact cells (*See*, Office Action at page 3; Aridor at page 1570), as such, Aridor, in fact, teaches away from the present invention which targets intact cells *in vivo*. As neither Kuby or Aridor teach or suggest a therapeutic agent comprising a molecule with a segment competent for importation of the molecule *in vivo* or methods of treating an allergic condition in a subject using the therapeutic agent, the combination of Kuby and Aridor does not produce the claimed invention nor does it contain a suggestion or motivation to combine Kuby and Aridor in such a way to achieve the claimed invention.

Lin generally discloses methods of importing biologically active molecules into a cell *in vitro*, *ex vivo* or *in vivo* by administering to the cell, a complex comprising an importation competent signal peptide linked to the biologically active molecule. However, out of the numerous possibilities of biologically active molecules and cell types, Lin only specifically teaches importation of the nuclear localization sequences of acidic FGF (aFGF) and NF-κB p50

[3] *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

and p65 subunits into NIH 3T3, baby hamster kidney-21, HUVEC and LE-II cells *in vitro* (*See*, Lin column 11, line 41 – column 17, line 50). Lin does not teach or suggest importation into mast cells and does not teach or suggest the administration of the therapeutic molecule of the present invention to treat an allergic condition in a subject *in vivo*. In contrast, Applicants submit that Lin teaches away from therapeutic uses of biologically active molecules linked to importation competent signal peptides *in vivo* to treat an allergic condition in a subject. Specifically, Lin discloses that, when compared to aFGF not linked to an importation peptide, the importation peptide comprising aFGF is less mitogenicically potent as shown by thymidine incorporation and DNA synthesis assays (*See*, Lin column 15, line 59 – column 16, line15; Figure 1; Table 2). In fact, the decreased mitogenic potency is significant, as aFGF not linked to an importation peptide at a concentration of 15 ng/ml stimulates DNA synthesis at a level more than twice that of the importation peptide comprising aFGF at 100 ug/ml (a concentration 10,000 fold greater than the concentration of aFGF).

In contrast to the Examiner's assertion, Lin does not cure the deficiencies of Kuby and Aridor. In combination, Kuby, Aridor and Lin do not teach or suggest the *in vivo* administration of the therapeutic compound of the present invention into mast cells in a subject. Moreover, the references in combination do not teach methods of treating an allergic condition in a subject by the *in vivo* administration of the therapeutic compound of the present invention into mast cells.

Applicants submit that the Examiner has improperly applied hindsight in combining the prior art references in reaching the present obviousness rejection. Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.[4] In making the assessment of differences, 35 U.S.C. § 103 specifically requires consideration of the claimed invention "as a whole." Inventions typically are new combinations of existing principles or features (noting that "virtually all [inventions] are combinations of old elements.").[5] The "as a whole" instruction in 35 U.S.C. § 103 prevents evaluation of the invention part by part.[6] Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious.[7] This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would

[4] *Crown Operations Int'l, LTD v. Solutia Inc.*, 289 F.3d 1367 (Fed. Cir. 2002)
[5] *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693 (Fed. Cir. 1983)
[6] *Ruiz v. A.B. Chance Co.*, 2004 U.S. App. LEXIS 1325 (2004).
[7] *Id.*

discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention.[8] Thus, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor.[9] When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.[10] Therefore, as discussed *supra*, Applicants submit that the combination of Kuby, Aridor and Lin do not produce the claimed invention nor do Kuby, Aridor and Lin contain a suggestion or motivation to combine them in such a way to achieve the claimed invention.

Reasonable Expectation of Success:

Further, Applicants submit that the standard applied to Kuby, Aridor and Lin by the Examiner is not an *prima facie* case of obviousness standard (See, MPEP § 2143) but rather an obvious to try standard. It has been held that what was obvious to try was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of a the claimed invention or how to achieve it.[11] Thus, although the prior art may suggest the desirability of the result attained by the invention, and encourage researchers to undertake work directed toward this result in a promising field, the prior art must also provide specific guidance as to the particular form of the invention and how to achieve it.[12]

A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success."[13] Further, "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."[14]

The reasonable expectation of success requirement has two distinct components. First, the guidance that the reference provides must be sufficiently specific to direct the attention to

[8] *Id.*
[9] *Id.*
[10] *Id.*
[11] *Id.*
[12] *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992).
[13] *In re Vaeck*, 947 F.2d at 493.
[14] *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

one skilled in the art to the selection of parameters and choices necessary to obtain the invention.[15] Prior art does not satisfy this requirement if it is necessary to vary all parameters, or to try each of numerous possible choices, in order possibly to arrive at successful results.[16] The second and related element of a reasonable expectation of success is that the prior art suggesting the desirability of the invention must enable one of ordinary skill in the art to produce it.[17]

Kuby generally discloses mast cells and various drug therapies. Aridor only discloses the inhibition of exocytosis by the introduction of a Gai_3 peptide to permeabilized mast cells *in vitro*. Also, Aridor merely discloses inhibition of exocytosis *in vitro*, Aridor does not teach methods of treating an allergic condition *in vivo* in a subject. Further, Aridor teaches away from the present invention which targets intact cells *in vivo* by disclosing that the Gai_3 peptide was ineffective at inhibiting exocytosis when added to intact cells. Lin generally discloses methods of importing biologically active molecules into a cell *in vitro*, *ex vivo* or *in vivo* by administering to the cell, a complex comprising an importation competent signal peptide linked to the biologically active molecule. However, Lin only specifically teaches the importation of two biologically active molecules into three cell types. The skilled artisan would readily recognize that the active molecules and cell types disclosed in Lin are vastly different from anti-allergic segments and the mast cells of the instantly claimed invention. Further, Lin teaches away from the instant claimed invention (treating an allergic condition in a subject *in vivo*) when it discloses the limited mitogenic potency of the disclosed importation peptide comprising aFGF in thymidine incorporation and DNA synthesis assays.

Thus, as the combination of Kuby, Aridor and Lin does not teach or suggest the administration of the therapeutic compound of the present invention into mast cells *in vivo* to treat an allergic condition in a subject, and in fact teaches away from the claimed invention, Applicants submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Kuby, Aridor and Lin to reach the presently claimed invention.

Unexpected Results:

Moreover, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made involves factual findings with respect to

[15] *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).
[16] *Id.*
[17] *Id.*

secondary considerations, including unexpected results.[18] Applicants submit that one of ordinary skill in the art would not have expected the *in vivo* importation of an anti-allergic agent into a mast cell in a subject to treat an allergic condition. Mast cells are unique. They are unique in that, following activation, they release (exocytosis) their contents (*i.e.* mediators of the inflammatory reaction). It is therefore not obvious or predictable that mast cells, *in vivo*, would incorporate and retain an anti-allergic agent instead of releasing them following allergen stimulation in a subject. Further, besides the *in vivo* functional uniqueness of mast cells, mast cells are quite different, in culture *in vitro* or *ex vivo*, from the cells disclosed in Lin. Mast cells are not fixed culture cells as the cells in Lin but rather are suspension culture cells. The skilled artisan would readily determine that this feature makes experimentation and extrapolation of data between fixed and suspension cultures much more difficult as many assays which are successful in fixed cultures fail in suspension cultures. It is therefore not obvious or predictable that mast cells in a subject, *in vivo*, would incorporate the molecule of the claimed invention.

In view of the above, withdrawal of the rejection under § 103 is respectfully requested.

B. Claims 30, 31 and 47 stand rejected under 35 U.S.C §103 as being unpatentable over Kuby in view of Aridor and Lin and further in view of U.S. Pat. No. 6,103,692 to Avruch (hereafter referred to as "Avruch").

The Examiner states that Avruch teaches that succinylation of peptides increases the ability of the peptide to pass through the cell membrane and into the cell and thus one of ordinary skill in the art would have been motivated to succinylate the peptide made obvious by Kuby, Aridor and Lin (*See*, Office Action at page 4). Applicants traverse.

As discussed *supra*, Applicants submit that one of ordinary skill in the art would not have been motivated to combine the teachings of Kuby, Aridor and Lin to reach the present invention. Avruch generally discloses amino-terminal blocking groups (including succinyl) to inhibit and reduce peptide cleavage, which would have the additional benefit of enhancing passage of the peptide through the hydrophobic cellular membrane and into the cell. Avruch does not teach *in vivo* administration, mast cells, anti-allergenic agents or methods of treating an allergic condition in a subject with the claimed therapeutic molecule, as such, Avruch does not cure the deficiencies of Kuby, Aridor and Lin and one of ordinary skill in the art would not be motivated to combine Kuby, Aridor, Lin and Avruch to achieve the present invention.

Thus, Applicants respectfully request withdrawal of the present rejection.

[18] *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

Matthew Pavo 50,572

Ivor R. Elrifi, Esq., Reg. No. 39,529
Attorney for Applicant(s)
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No.: 30623

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